INVEST SECURITIES

BIOTECH

ORYZON GENOMICS

BUY

TARGET PRICE : 9,3€ +144%

INITIATION OF COVERAGE

A NEW WAVE

We are initiating coverage of ORYZON GENOMICS this morning with a BUY opinion and a target price of €9,3. ORYZON is a Spanish biotech specializing in the treatment of cancers and neurodegenerative diseases. Based on its epigenetic (regulatory system controlling gene expression) platform, the group's two leading products, ORY-1001 and ORY-2001, are currently in phase IIa trials in four indications: Alzheimer's, multiple sclerosis, SCLC and AML. Initial intermediate results are expected in mid-2019.

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The epigenetic platform remains the basis of development

Oryzon's technological platform is based on the concept of "epigenetics", the study of a regulatory system that controls the expression of genes in order to understand their uses within the cell. The regulation of gene transcription is a key factor in the production of proteins and cellular differentiation and is significant factor in the onset and progression of certain diseases such as cancer and neurodegenerative diseases. Additionally, the identification of complementary biomarkers could constitute one of the differentiating factors in Oryzon's approach.

ORY-2001 in Alzheimer's disease and multiple sclerosis

We estimate that ORY-2001 is the product with the greatest potential, even if its area of development suggest a certain degree of caution. ORY-2001 is a bispecific inhibitor: inhibitor of lysine specific demethylase 1 (LSD1) and inhibitor of monoamine oxidase B (MAO-B). Initial animal tests have clearly shown the interest of this orally-administered LSD1 inhibitor: increase in the survival times and improvement in several behavioral and motor parameters. Despite the enormous market in Alzheimer's disease, we believe that the principal indication could be secondary progressive multiple sclerosis, where no drug has been approved as of now. In a rapidly evolving therapeutic area (arrival of Ocrevus in primary progressive MS, loss of patents by Gilenya and Aubagio over the short term), we believe that, if the results in this phase prove positive, the company could become a potential takeover target.

ORY-1001 in blood and solid cancers

After having recovered the rights to ORY-1001, Oryzon worked to launch two phases IIa studies at the beginning of this year, one in acute myeloid leukemia and the other in small cell lung cancer. The activation of oncogenes and the deactivation of tumor suppressor genes have long been established as basic mechanisms causing cancer. Oryzon is targeting more particularly a sub-category of AML: mixed lineage leukemia (MLL). A study published in *CELL* showed that the inhibition of LSD1 could enhance the immunogenicity of tumors and the infiltration of T cells. In parallel, another phase IIa study is in the process of being launched in small cell lung cancer.

.../...

in € / share	2016e	2017e	2018e
Adjusted EPS	-0,22	-0,22	-0,31
chg.	*n.s.*	*n.s.*	*n.s.*
estimates chg.	*n.s.*	*n.s.*	*n.s.*

au 31/12	2016e	2017e	2018e
PE	n.s.	n.s.	n.s.
EV/Sales	81,11x	83,93x	87,90x
EV/EBITDA	n.s.	n.s.	n.s.
EV/EBITA	n.s.	n.s.	n.s.
FCF yield*	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.

* After tax op. FCF before WCR

key points	
Share price (€)	3,8
Number of Shares (m)	34,2
Market cap. (€m)	130
Free float (€m)	84
ISIN	ES0167733015
Ticker	ORY-ES
DJ Sector	Health Technology

	1m	3m	Ytd
Absolute perf.	+6,1%	+42,7%	+45,7%
Relative perf.	+12,2%	+49,8%	+54,9%

Source : Factset, Invest Securities estimates

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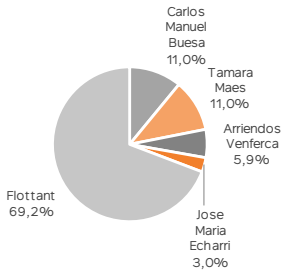
INVESTMENT CASE

ORYZON IS A SPANISH BIOTECH SPECIALIZING IN THE TREATMENT OF CANCERS AND NEURODEGENERATIVE DISEASES. IN ALL ITS DEVELOPMENT PROGRAMS, THE COMPANY IDENTIFIES BIOMARKERS THROUGH ITS GENETIC AND PROTEOMIC PLATFORMS IN ORDER TO DEVELOP SMALL MOLECULE DRUGS.

FINANCIAL DATA

Shareholders



Share information	2015	2016	2017	2018e	2019e	2020e	2021e
Published EPS (€)	-0,04	-0,19	-0,15	-0,28	-0,22	-0,22	-0,31
Adjusted EPS (€)	**-0,04**	**-0,19**	**-0,15**	**-0,28**	**-0,22**	**-0,22**	**-0,31**
Diff. I.S. vs Consensus	*+320,5%*	*+12,6%*	*-0,3%*	*+72,4%*	*+2,7%*	*n.s.*	*n.s.*
Dividend							

Valuation ratios	2015	2016	2017	2018e	2019e	2020e	2021e
P/E	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EV/Sales	9,01x	16,36x	32,10x	78,29x	81,11x	83,93x	87,90x
VE/EBITDA	13,2x	37,8x	124,8x	n.s.	n.s.	n.s.	n.s.
VE/EBITA	13,2x	37,8x	124,8x	n.s.	n.s.	n.s.	n.s.
Op. FCF bef. WCR yield	0,5%	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Op. FCF yield	1,2%	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Div. yield (%)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

NB : valuation based on annual average price for past exercise

Entreprise Value (€m)	2015	2016	2017	2018e	2019e	2020e	2021e
Share price in €	*3,2*	*3,0*	*4,6*	*10,0*	*10,0*	*10,0*	*10,0*
Market cap.	76	85	156	342	381	381	381
Net Debt	-12	-3	-17	-5	-32	-20	-3
Minorities	0	0	0	0	0	0	0
Provisions/ near-debt	0	0	0	0	0	0	0
+/- Adjustments							
Entreprise Value (EV)	**65**	**82**	**139**	**337**	**349**	**361**	**378**

Income statement (€m)	2015	2016	2017	2018e	2019e	2020e	2021e
Sales	7	5	4	4	4	4	4
chg.	*-53,8%*	*-30,3%*	*-13,8%*	*-0,4%*	*+0,0%*	*+0,0%*	*+0,0%*
EBITDA	5	2	1	-12	-12	-12	-17
EBITA	**5**	**2**	**1**	**-12**	**-12**	**-12**	**-17**
chg.	***ns***	***-55,7%***	***-48,8%***	***n.s.***	***n.s.***	***n.s.***	***n.s.***
EBIT	0	-5	-4	-12	-12	-12	-17
Financial result	-1	-1	-1	0	0	0	0
Corp. tax	0	0	0	3	3	3	3
Minorities+affiliates							
Net attributable profit	-1	-5	-5	-9	-9	-9	-14
Adjusted net att. profit	**-1**	**-5**	**-5**	**-9**	**-9**	**-9**	**-14**
chg.	***ns***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***

Cash flow statement (€m	2015	2016	2017	2018e	2019e	2020e	2021e
EBITDA	5	2	1	-12	-12	-12	-17
Theoretical Tax / EBITA	-1	-1	0	3	3	3	4
Capex	-3	-8	-4	0	0	0	0
Operating FCF bef. WCR	**0**	**-6**	**-4**	**-9**	**-9**	**-9**	**-13**
Change in WCR	0	0	0	0	0	0	0
Operating FCF	**1**	**-6**	**-4**	**-9**	**-9**	**-9**	**-13**
Acquisitions/disposals	3	1	5	0	0	0	0
Capital increase/decrease	15	0	17	0	39	0	0
Dividends paid	0	0	0	0	0	0	0
Other adjustments	-4	8	-5	-3	-3	-3	-4
Published FreeCash Flow	**15,8**	**2,6**	**12,9**	**-12,1**	**26,9**	**-12,1**	**-17,1**

Balance Sheet (€m)	2015	2016	2017	2018e	2019e	2020e	2021e
Assets	18	21	25	28	30	33	36
Intangible assets/GW	15	19	22	22	22	22	22
WCR	-2	-1	-8	-8	-8	-8	-8
Group equity capital	28	23	34	25	55	45	31
Minority shareholders							
Provisions	0	0	0	0	0	0	0
Net financial debt	**-11,6**	**-2,6**	**-17,2**	**-5,0**	**-31,9**	**-19,8**	**-2,7**

Financial ratios	2015	2016	2017	2018e	2019e	2020e	2021e
EBITDA margin	68,2%	43,3%	25,7%	n.s.	n.s.	n.s.	n.s.
EBITA margin	68,2%	43,3%	25,7%	n.s.	n.s.	n.s.	n.s.
Adjusted Net Profit/Sales	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ROCE	30,7%	10,8%	6,4%	n.s.	n.s.	n.s.	n.s.
ROE adjusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gearing	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ND/EBITDA (in x)	-2,4x	-1,2x	-15,5x	n.s.	n.s.	n.s.	n.s.

Source : company, Invest Securities Estimates

Next events

Q2 2019: Résultats phase IIa ORY1001
mi 2019: Résultats phase IIa ORY2001

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SOMMAIRE

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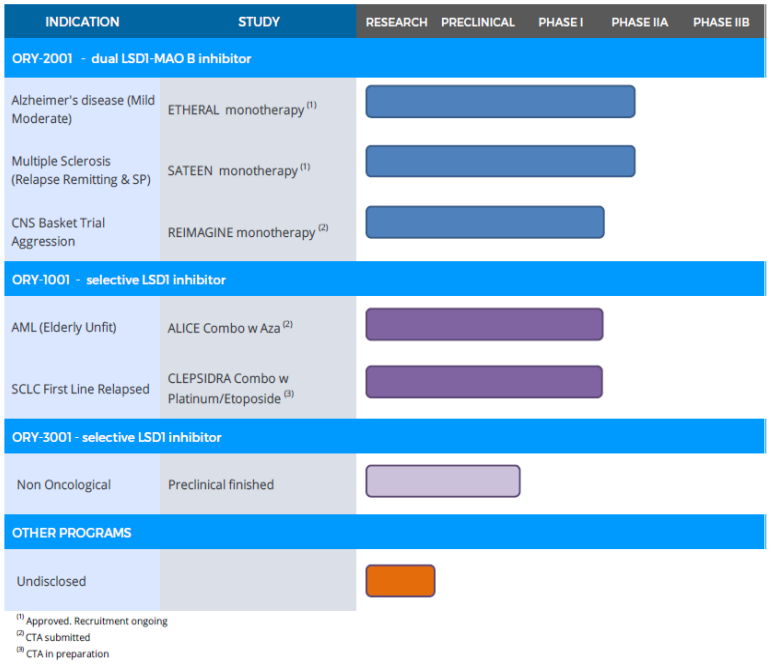
Introduction

ORYZON is a Spanish biotech specializing in the treatment of cancers and neurodegenerative diseases. In all its development programs, the company identifies biomarkers through its genetic and proteomic platforms in order to develop small molecule drugs.

EXTENSIVE PIPELINE : 2 PROGRAMS IN CLINIC WITH MULTIPLE INDICATIONS

- ✓ A Productive Epigenetic Platform
- ✓ A strong focus on LSD1
- ✓ 3 Different LSD1 inhibitors in development
- ✓ Additional programs on other targets



Source: Oryzon Genomics

An epigenetic platform as the basis of clinical development

Oryzon's technological platform is based on the concept of "epigenetics", the study of a regulatory system that controls the expression of genes in order to understand their uses within the cell. The regulation of gene transcription is a key factor in the production of proteins and cellular differentiation.

In simple terms, this regulation is mediated by "selective and reversible" modifications of DNA and proteins, particularly histones. These modifications are caused by enzymes whose alteration leads to disease in humans. The modifications of histones caused by specific enzymes disrupts the translation of the DNA. The goal is therefore to target these enzymes.

Oryzon is notably focusing on the inhibition of lysine specific demethylase 1 (LSD1). This enzyme modifies the histones that eliminate methyl groups. It regulates the expression of genes linked to the onset and progression of diseases such as cancer, viral infections, neurodegenerative diseases etc.

This epigenetic platform is based on genomics and bioinformatics as well as the identification of biomarkers relating to the validation of the mode of action.

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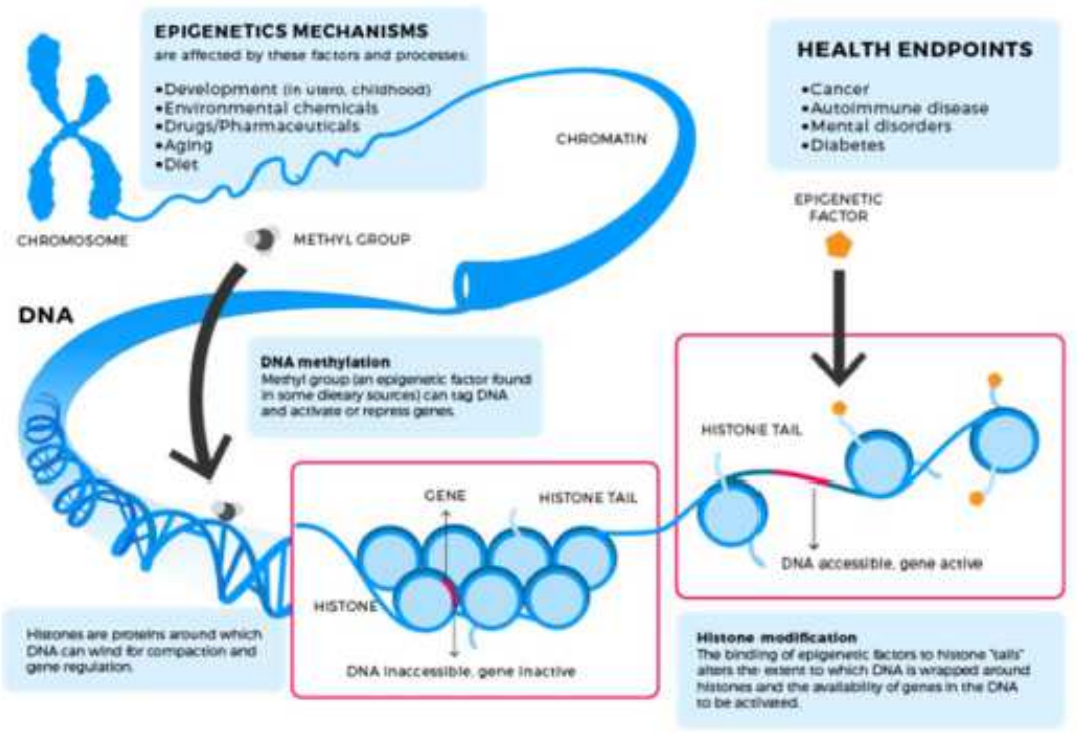

Source: Oryzon Genomics

Why target histone demethylases?

As indicated above, Oryzon is currently focusing on the identification of genetic alterations. These modifications in the expression of genes without changes in the nucleotide sequences of the DVA are in principle one of the factors in the evolution and progression of diseases. The DNA is wrapped around four proteins called histones. The regulation of the transcription notably involves modifications in the how tightly the DNA is wrapped around these histones. The best known modifications are currently acetylation, methylation and phosphorylation.

ORYZON is currently studying the state of methylation of the histone, which has shown a high level of activity in cell proliferation and on the level of the central nervous system. The best known method involved in this approach remains the acetylation of the histone, accomplished by the balancing of two enzymes, the histone acetyltransferases (HAT) and the histone deacetylases (HDAC), which add or remove an acetyl group from the lysine. When the lysine is deacetylated, it is referred to as charged, reducing the DNA compaction and favoring its transcription. As such, a breakdown in the equilibrium between HAT and HDAC contributes in principle to the alteration of the expression of genes. The concept here is identical. Oryzon is working on the lysine specific demethylase 1 (LSD1) histone, also known as KDM1A. The challenge is to erase the methyl marks on mono- and dimethyl-H3K4 (histone H3 lysine 4) and H3K9 (histone H3 lysine 9).

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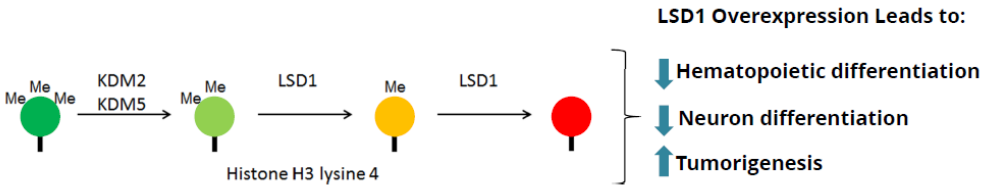

Source: Oryzon Genomics

The erasing of methyl marks (demethylation) regulates the expression of genes that are important in the onset and progression of certain diseases such as cancer and neurodegenerative diseases. The identification of complementary biomarkers could also be a differentiating factor in Oryzon's approach.

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1 – SPECIALIZATION IN THE CENTRAL NERVOUS SYSTEM (CNS)

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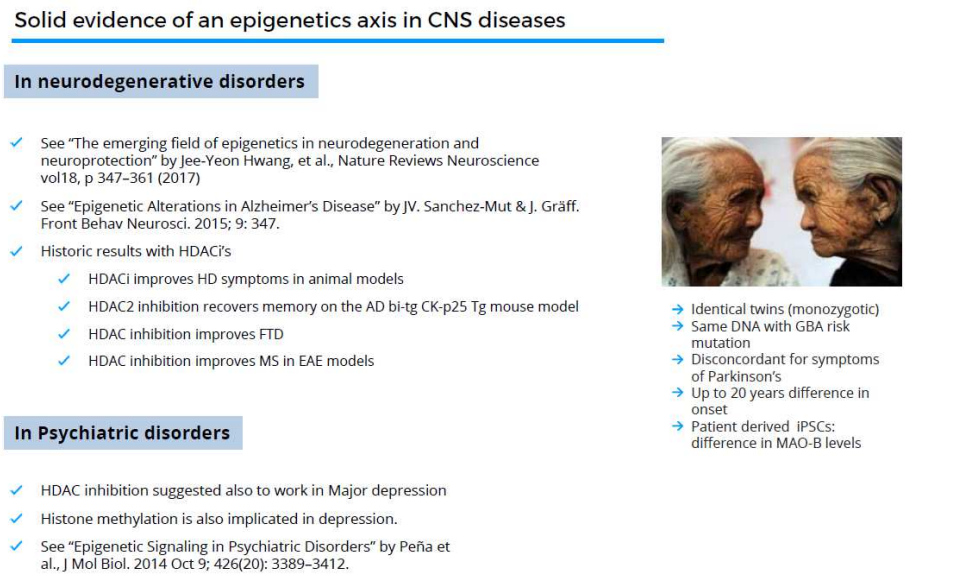
1 – Specialization in the central nervous system (CNS)

The central nervous system (CNS) remains one of the most difficult therapeutic areas to address due to the complexity of the signaling pathways and the mechanisms of action. CNS disorders continue to represent a major cause of morbidity and consequently represent a major source of revenues for the pharmaceutical companies. Nevertheless, despite the promising results shown by recent phase II results from Biogen and Eisai (BAN2401), the number of failures in all stages of clinical development is substantial, as recently illustrated by the halt of the phase III study of Lanabecestat (Lilly and AstraZeneca) in Alzheimer's disease .

In 2018, drugs for treatment of central nervous system disorders generated around $80bn in revenues (*source* : *Evaluate Pharma*). The risk / reward trade-off is consequently high attractive.



Source : Oryzon Genomics

1.1 The LSD1 – MAO-B pathway in Alzheimer's, Parkinson's and other dementias

We estimate that ORY-2001 is the product with the greatest potential, even if its area of development suggest a certain degree of caution. Currently in phase IIa trials, ORY-2001 targets the LSD1 / MAO-B pathway in potentially different indications including Alzheimer's and multiple sclerosis as well as a range of CNS disorders potentially linked to a modification in aggressiveness.

ORY-2001 is a dual inhibitor: inhibitor of lysine specific demethylase 1 (LSD1) and inhibitor of monoamine oxidase B (MAO-B).

Monoamine oxidase B (MAO-B) is an enzyme that is regularly studied in the treatment of neurological disorders (Parkinson's). MAO-B converts certain amino acids into toxins that can cause damage on the level of the neurons. Abnormally high accumulation of MAO-B has been observed in neurodegenerative diseases. As discussed previously, lysine specific demethylase 1 (LSD1) is an enzyme that erases methyl groups from the histone H3 lysine that organizes the nucleosomes. An epigenetic modification would lead to repression of the transcriptional activities of the targeted genes.

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1 – Specialization in the central nervous system (CNS)

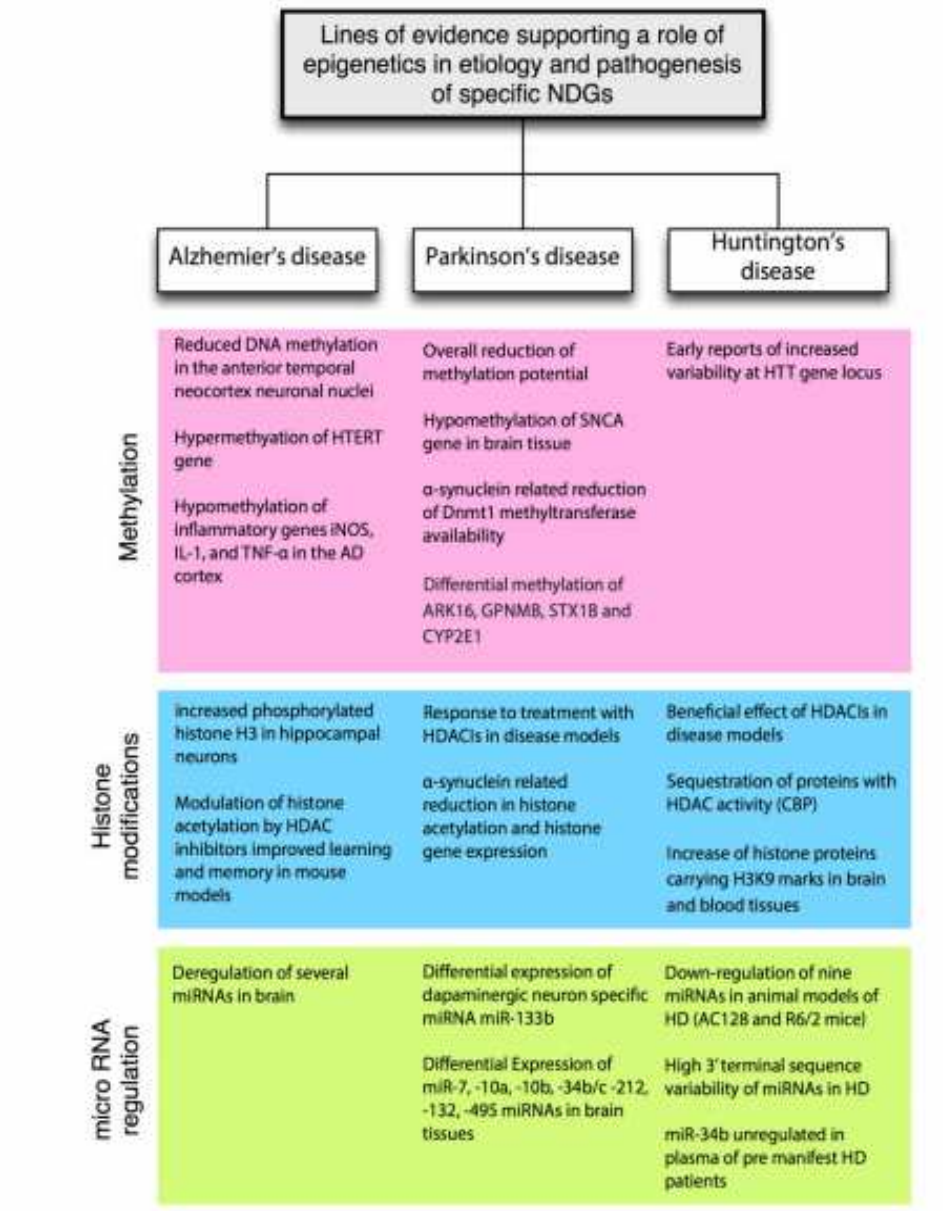

Figure 2. Key epigenetic changes in PD, AD and HD

Source: Luca Lovrečić, et al., 2013, *The Role of Epigenetics in Neurodegenerative Diseases*

In contrast to "traditional" HDACs, Oryzon's drug does not show a pleiotropic effect, i.e. it appears to a have a more specific activity with a selective inhibition of LSD1 and MAO-B.

The initial animal trials have demonstrated the substantial interest of this orally-administered LSD1 inhibitor: improvement in memory and several behavioral and motor parameters.

This first trial in mice showed both the immediate and continued impact of the drug on the organism. While the cognitive function fell over time, the mice nevertheless returned to a level similar to the normal decline following the oral administration of the drug, regardless of whether treatment was administered after five, six or eight months of progression.

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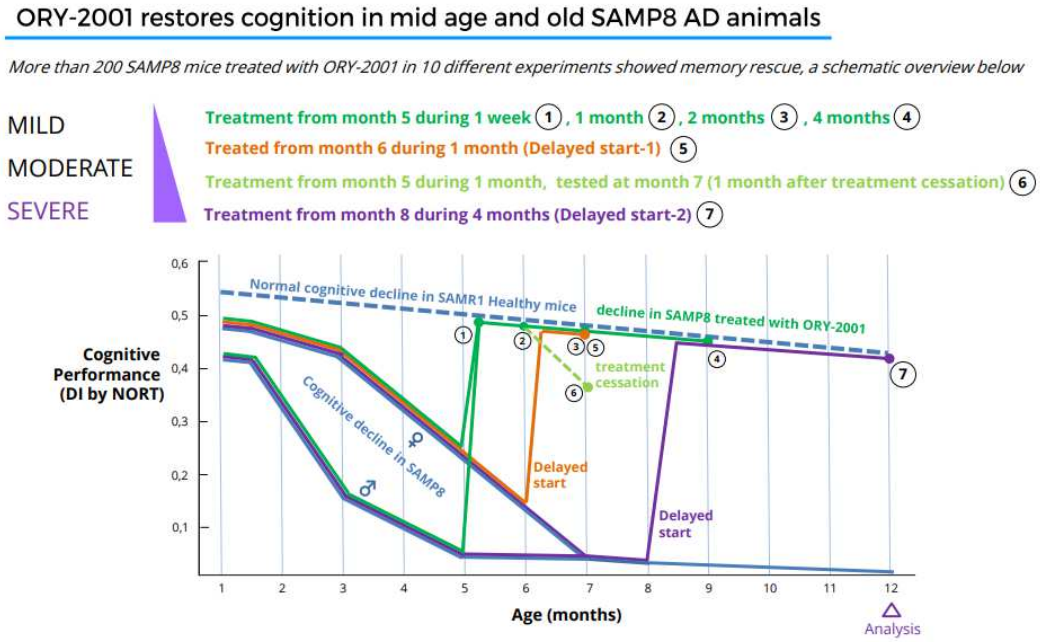

Results suggestive of Disease modifying potential

Source: Oryzon Genomics

Additionally, we can see that despite the end of the treatment, the effect continued for another month.

ORY-2001 substantially reduced the expression of a sub-ensemble of genes in SAMP8 mice linked to the immune reaction and inflammation, including the S100A9 chains and the beta receptors of T lymphocytes. At the same time, an improvement in cognitive function was observed as the result of the regulation of certain specific genes (memory rescue).

The reduction in the pro-inflammatory protein S100A9 in the hippocampus induced by ORY-2001 is particular interesting given that S100A9 is a key protein in neurodegeneration linked to inflammation. An abnormally high concentration of S100A9 has been observed in patients with post-operatory cognitive dysfunction, traumatic cerebral lesions and neuro-inflammatory diseases such as MS etc.

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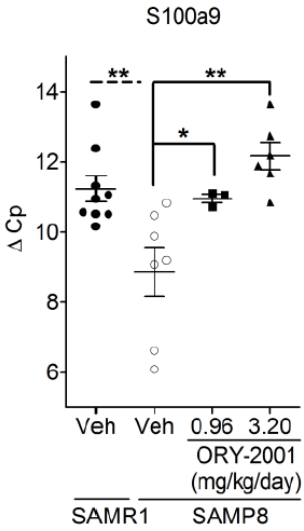
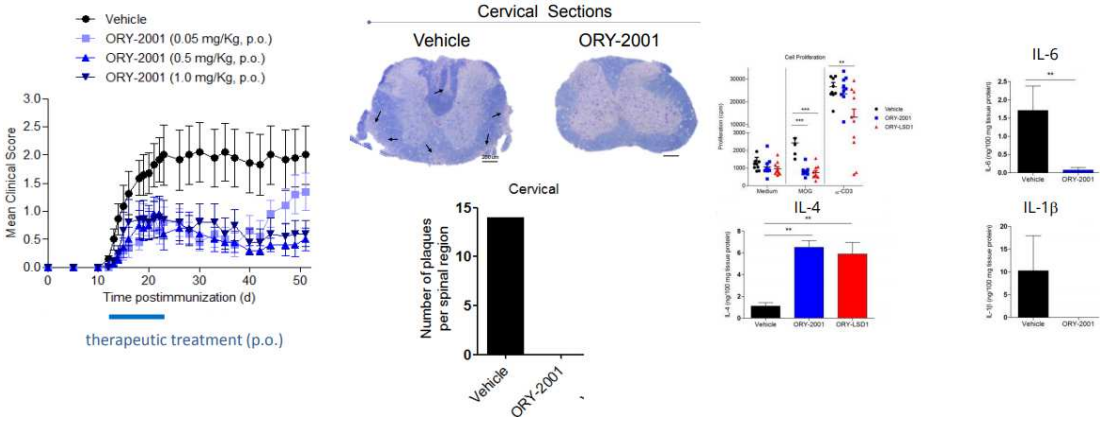


Source: Oryzon Genomics

ORY-2001 in principle has a "protective" action in the brain and the CNS during acute inflammatory stress. Again in animals, the immune infiltration in the spinal cord is substantially reduced and the demyelination is limited, thereby reducing the clinical score.



Source: Oryzon Genomics

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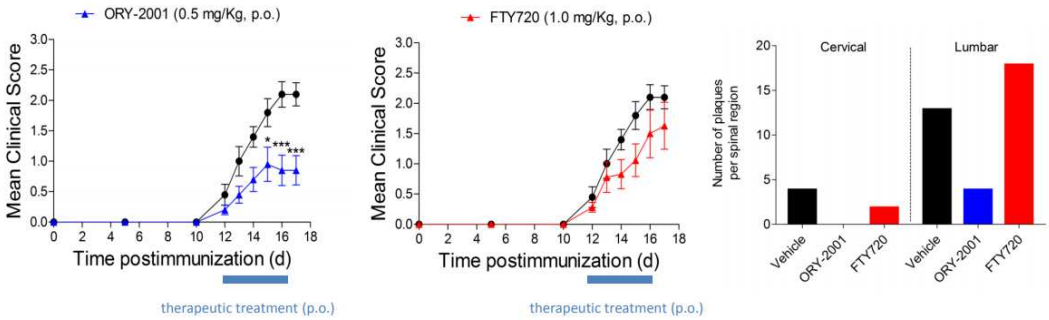
1 – Specialization in the central nervous system (CNS)

ORY-2001 is more protective and/or acts faster than Fingolimod in the effector phase of the EAE model

Effects of ORY-2001 and FTY720 (fingolimod) in the **EAE effector phase** (therapeutic setting):



- ✓ ORY-2001 clearly reduced the mean clinical score, FTY720 exhibited only a tendency
- ✓ ORY-2001 is more effective and/or faster acting than FTY720 in the effector phase

Source: Oryzon Genomics

In patients suffering from Alzheimer's, cognitive decline is often accompanied by aggressiveness, agitation, psychosis, depression and apathy. SAMP8 mice show more aggressive behavior than SAMR1 mice. Treatment with ORY-2001 significantly reduces the aggression parameters and leads to levels equivalent to those of SAMR1 mice in the control group.

		Relevance in some CNS disorders					
ORY-2001 in PC models		AD	MS	PD	HD	ASD	Depression
+	Cognition / Memory	+		+	+	+	
+	Neuroprotection	+	+	+	+	+	+
+	Neuroinflammation	+	+	+	+	+	?
+	Social Withdrawal / Apathy	+	+	+	+	+	+
+	Sociability					+	+
+	Aggression/Agitation	+		+	+	+	+

These data may substantially broaden the potential clinical development of ORY-2001 beyond the current indications of AD and MS that the company is initially advancing in clinical trials

Source: Oryzon Genomics

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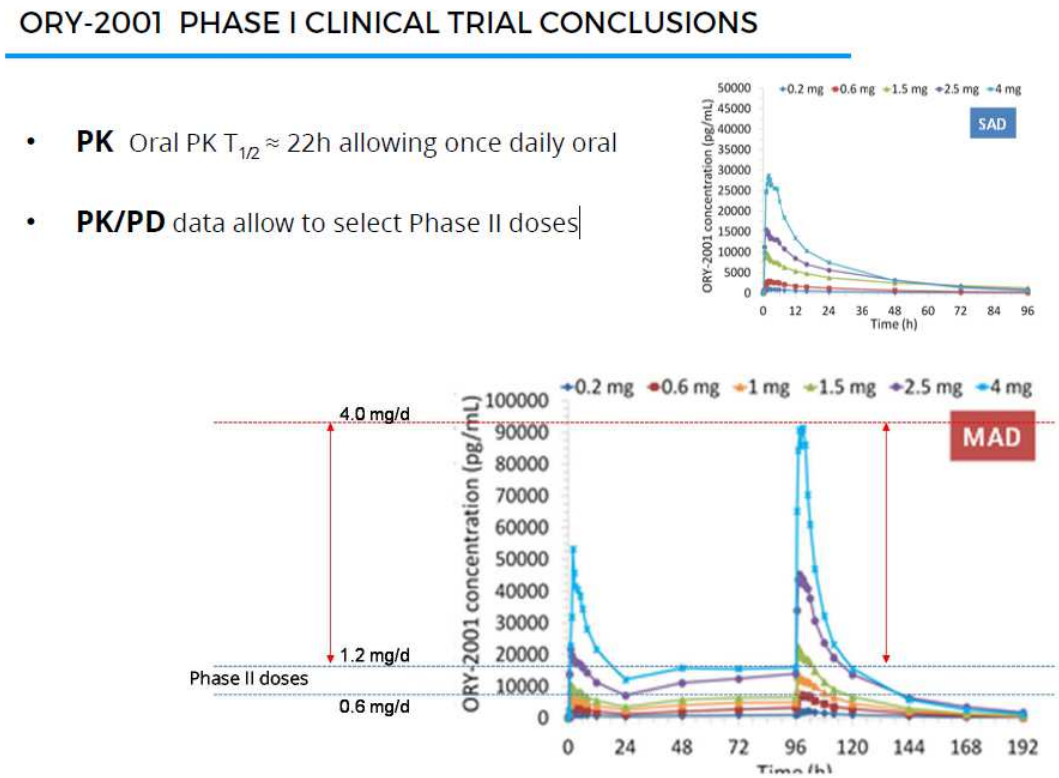
1 – Specialization in the central nervous system (CNS)

1.2 Initial clinical results justifying a phase IIa study

ORY-2001 has up to now met the selection criteria set by the company: pharmacokinetics allowing oral administration and, most importantly, safety of use allowing the continuation of development in phase II.

ORY-2001 has effectively already been administered to over 100 healthy volunteers without any questions being raised concerning its safety of use. ORY-2001 has been show to cross the blood-brain barrier in line with the concentration of the drug in the bloodstream The aspect would enable it to perform its LSD1 inhibition action on the level of the brain.

The other factor is its distribution in the organism. The initial results have served to confirm its development in the form of once-daily oral administration. The half-life of the drug is effectively around 22 hours. This factor is of primordial importance in terms of predicting initial commercial success given that the CNS market is dominated by oral treatments.



Source: Oryzon Genomics

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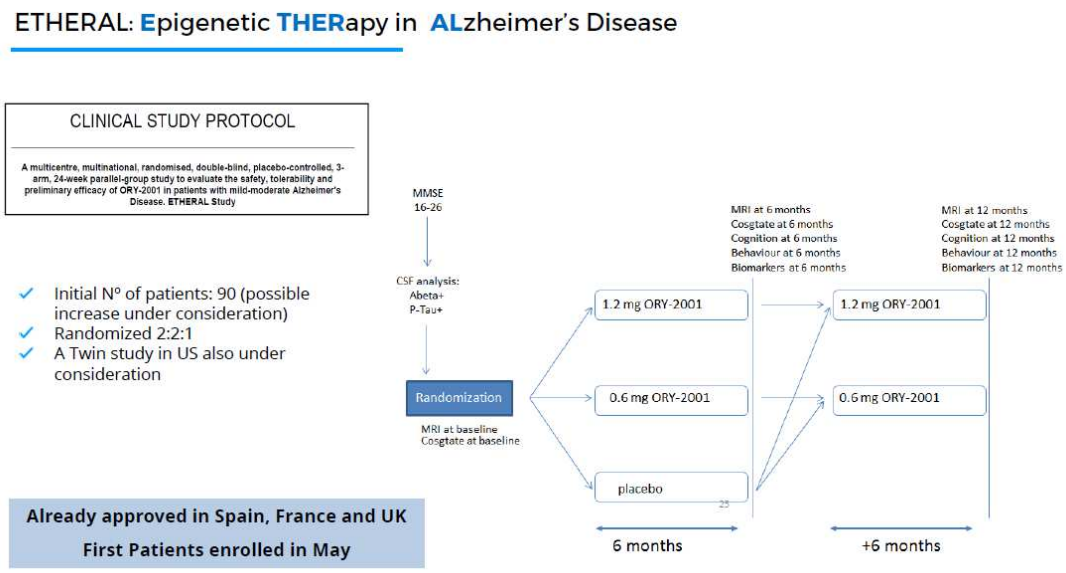
1 – Specialization in the central nervous system (CNS)

1.3 Launch of two phase IIa studies in Alzheimer's and multiple sclerosis

The first patients for the phase IIa study in the treatment of Alzheimer's were recruited in Spain last May.

This study, called ETHERAL (Epigenetic THERapy in ALzheimer's disease), will be conducted in different European hospitals and has been designed as a randomized double blind study with a placebo control group and three arms, running 26 weeks in parallel groups in order to evaluate the safety and tolerability of ORY2001 in patients suffering from mild / moderate Alzheimer's disease. The secondary endpoints will be extremely interesting to analyze (keeping in mind the number of patients included): parameters concerning the stages of progression of the disease, including alterations in memory and behavior.

This study will include 90 patients. A parallel study could be launched in the United States over the near future. In patients suffering from Alzheimer's and other neurodegenerative disorders, cognitive decline is accompanied by episodes of agitation, aggression, psychosis, apathy and depression. As discussed above, preclinical studies have shown that ORY-2001 appears to restore memory as well as reducing the exacerbated aggressiveness and improving sociability in different mice models.



Source : Oryzon Genomics

A second phase IIa study of ORY-2001 has been launched in patients suffering from multiple sclerosis (MS). This study, called SATEEN, is currently being conducted in nine different hospitals and has been designed as a double-blind randomized study against placebo with three arms and running 36 weeks in parallel, also to evaluate safety and tolerability. The target population is made up of (i) patients suffering from relapsing-remitting multiple sclerosis (the largest portion of the market but where numerous patent expirations should lead to downward pressure in value terms) and (ii) patients suffering from secondary progressive multiple sclerosis, for which no treatment has been approved for the moment.

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1 – Specialization in the central nervous system (CNS)

SATEEN **A pilot study in MS**

SAfety, **T**olerability and **E**fficacy in an **E**PIGE**N**ETIC approach to treat Multiple Sclerosis

Randomised, double-blind, placebo-controlled, 3-arm, 36 weeks parallel-group study to evaluate the safety and tolerability of ORY-2001 in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS)

APPROVED by the AEMPS in October, 30th 2017

Spain only; 9 Hospitals; 24 patients (RR & SP);

FPI January 2018

expected LPO 1H2019

Source: Oryzon Genomics

1.4 A large market but with many pitfalls

1.4.1 Alzheimer's disease

Worldwide sales of the principal drugs used to treat Alzheimer's disease totaled around $2.5bn in 2017, keeping in mind that this figure does not include all the associated costs.

Alzheimer's affects 10% of the population aged over 65 years old, with around 35 million persons suffering from the disease throughout the world. The principal products at present are Aricept (Pfizer / Eisai), Namenda (Forest) and Exelon (Novartis). Alzheimer's disease corresponds to progressive dementia affecting cognition and behavior. It is characterized by a loss of short-term memory as well as deterioration in behavior and intellectual performances. The exact physiology is unknown and there is no cure. Alzheimer's disease is generally considered as an old age disease given that the majority of symptomatic cases are seen after the age of 65 years, even if the underlying disease can develop at a younger age.

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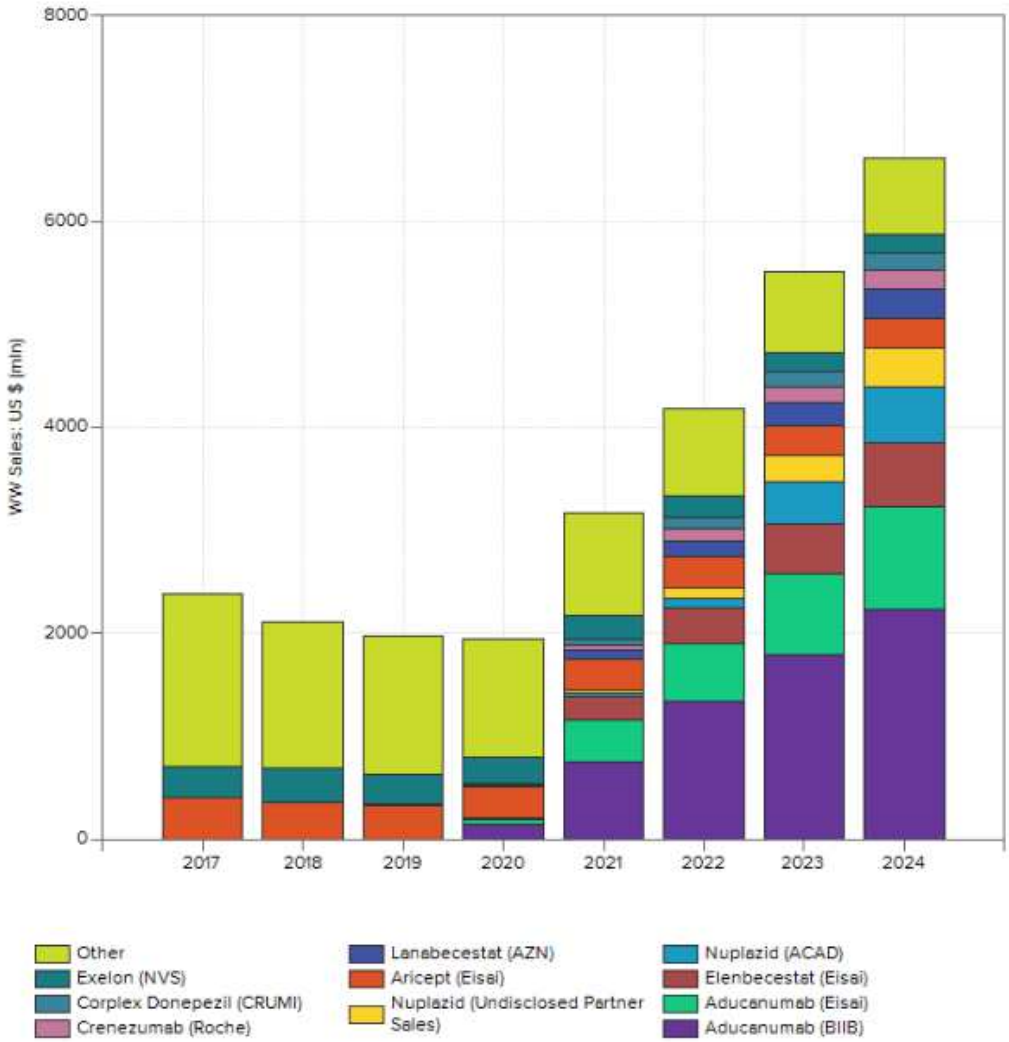
1 – Specialization in the central nervous system (CNS)



Source : Evaluate Pharma

The disease causes two types of lesions of the central nervous system:

- Dysfunction of the “Tau” protein

- The development of plaques due to a beta-amyloid protein that collects on the exterior of neurons

These lesions gradually multiply and invade the brain. The disease then becomes increasingly visible. As Alzheimer’s is a progressive disease, these changes build up over time.

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1 – Specialization in the central nervous system (CNS)

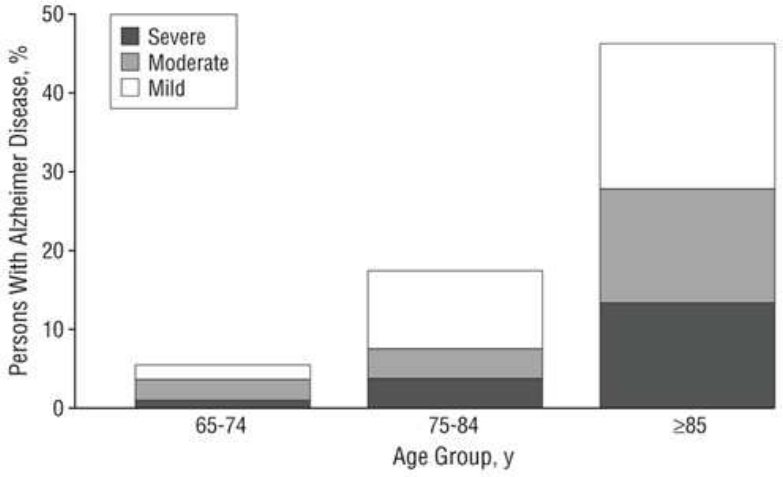
There are three stages of the disease in overall terms:

- **Mild stage:** the link between the short and long-term memory is more difficult to make (the hippocampus is affected).

- **Moderate stage:** other zones of the brain are affected, leading to problems with gestures, language and recognition.

- **Severe stage:** the lesions grow and patients lose their autonomy in terms of virtually all acts in their daily life.

The diseases advances in a progressive manner, with mild symptoms at first followed by moderate and severe symptoms in the oldest populations. It is estimated that the moderate stage of the disease in seen in 48% of the population, all ages combined.



Source: University of Tennessee Advanced Studies in Pharmacy

Acetylcholine plays a role in learning and short-term memory. In patients suffering from Alzheimer's disease, the concentration of acetylcholine and the number of neurons producing acetylcholine are reduced. Consequently, pharmacotherapy has focused on increasing the concentration of acetylcholine in the brain in order to improve the function of the remaining neurons. This is generally achieved by blocking the breakdown of acetylcholine by the acetylcholinesterase enzyme.

As we indicated in the introduction, this therapeutic area is a cemetery of aborted clinical development programs. We estimate that the difficulty lies in the primary endpoints linked to test scores that remain extremely subjective. The different test scores are based on interviews that measure the effectiveness compared to placebo. The most important test is the Alzheimer's Disease Assessment Scale (ADAS), with scores running from 0 to 70. The ADAS-Cog test can be conducted in 45 minutes and is more sensitive than the Mini-Mental State Examination (MMSE). The average deterioration in cognitive performances in the mild and moderate stages of the disease can be estimated by the loss of 2 to 4 points per year in the MMSE and 6 to 8 points per year in the ADAS-Cog.

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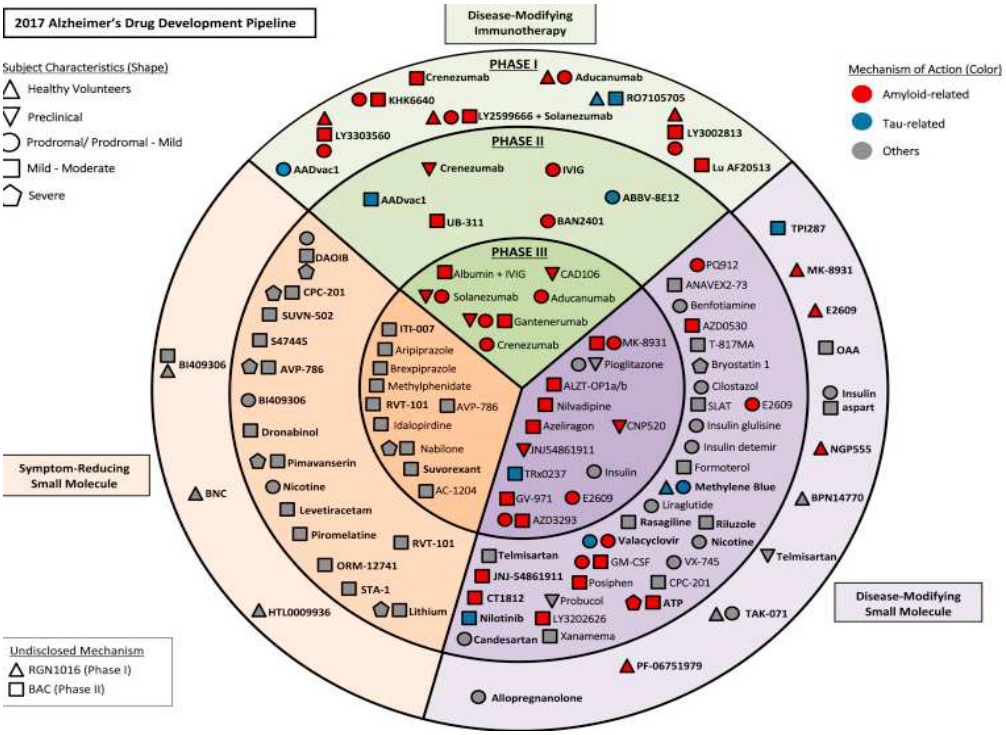
1 – Specialization in the central nervous system (CNS)

Several drugs targeting beta amyloid are under development. These drugs aim to either increase the clearance of B-amyloid plaques or inhibit enzymes leading to the synthesis of amyloid peptides. The results of the initial trials have not been very convincing (Elan, Pfizer, Lundbeck, Lilly). Roche also initially halted the development of gantenerumab on the basis of the results of a futility analysis. Nevertheless, while the product trials had been halted in 2015, Roche revived the program in 2017 directly in phase III with higher doses. The most recent failure was the halt of trials of Lanabecestat (AZN and Lilly). This decision was based on the recommendations of an independent committee, which concluded that the AMARANTH and DAYBREAK-ALZ studies were not likely to attain their primary endpoint, i.e. the change compared to the reference base of the cognitive evaluation scale for Alzheimer's disease (ADAS-Cog13).

However, a few major successes could be seen in this therapeutic area. In this regard, we would highlight the convincing results reported by Biogen at the beginning of the July. This phase II study evaluating BAN2401, an anti-amyloid beta protofibril antibody, showed statistically significant effectiveness at 18 months in terms of the slowing in the progression of the Alzheimer's disease composite score (ADCOMS) and a reduction in the accumulated amyloid in the brain. However a few questions remain regarding the composite endpoint and the population evaluated,



Source : Alzheimer's disease drug development pipeline: 2017; Jeffrey Cummings

1.4.2 Multiple sclerosis (MS)

The MS market exceeds $20bn and is made up of different classes of drugs. The interferons are prescribed as first-line treatment in order to reduce the inflammation associated with the disease. However, numerous players have entered this market over recent years, leading to a change in treatment. Aubagio from Sanofi (€1.5bn in 2017), Gilenya from Novartis ($3.2bn in 2017) and Tecfidera from Biogen ($4.2bn in 2017) can also be administered as first line treatment, particularly on the US market, where prescription indications are broader.

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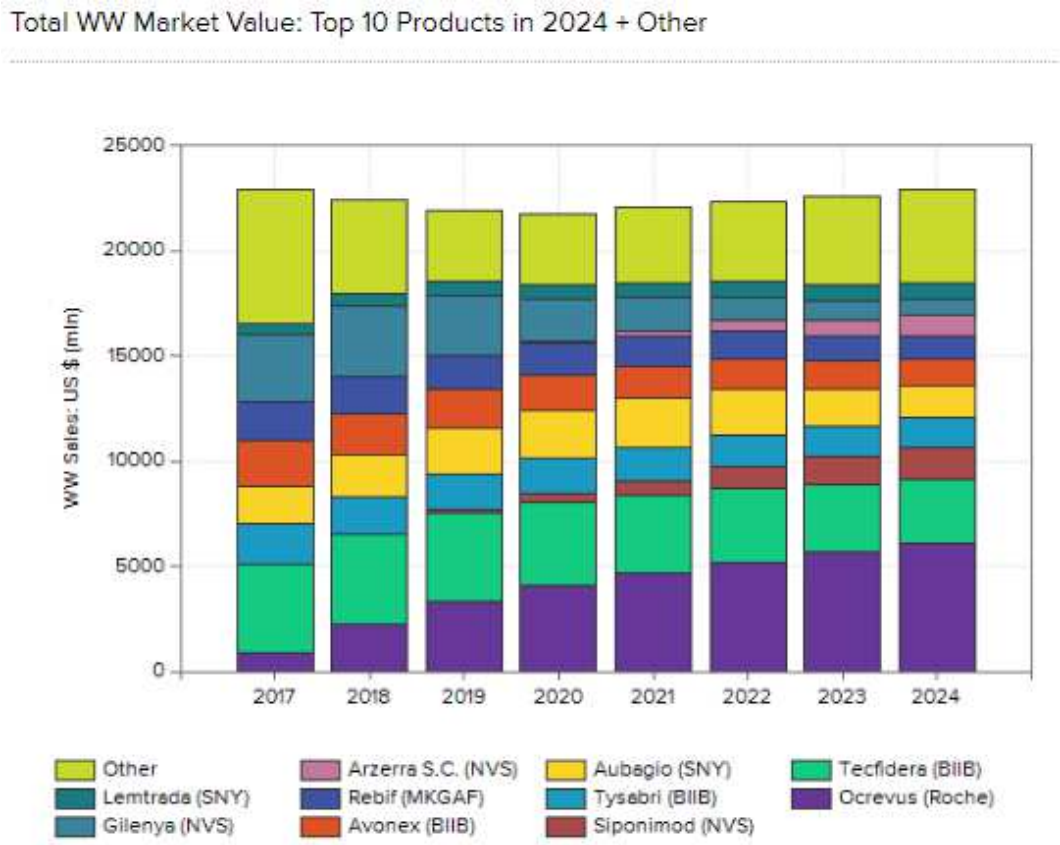
1 – Specialization in the central nervous system (CNS)



Source: Oryzon Genomics

The frequency of flare-ups varies for one individual to another. The succession over time of these flare-ups defines the form of the disease, referred to as “remitting” or “relapsing”.

For 30-50% of patients, the remitting phase changes after 15 years to a chronic progressive phase. When this chronic progressive phase follows a relapsing phase, the term secondary progressive is used.

In 15% of cases, the initial symptoms involve problems with walking without a gradual appearance of flare-ups. This is referred to as primary progressive MS. This form of the diseases is targeted by Roche’s Ocrevus.

Given the patent expirations over the near future (such as Gilenya followed by Aubagio as well as the interferons), we believe that the greatest challenge for ORY-2001 will be to target the secondary progressive form of the disease. At this point, no drug is approved for this indication. The first entrant could nevertheless be Medday, a French biotech that already distributes its biotin under a temporary authorization. Following positive phase II results, a phase III trial is underway. According to the principal published results, a total of 13 (12.6%) patients treated with MD1003 attained the principal endpoint vs. none with placebo (p = 0.005). Treatment with MD1003 also reduced the progression of the EDSS (*Expanded Disability Status Scale*) and improved the clinical impression. The effectiveness was maintained over the follow-up period and the safety profile of MD1003 was similar to that of placebo.

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2- ONCOLOGY, A CLEAR PATH AHEAD

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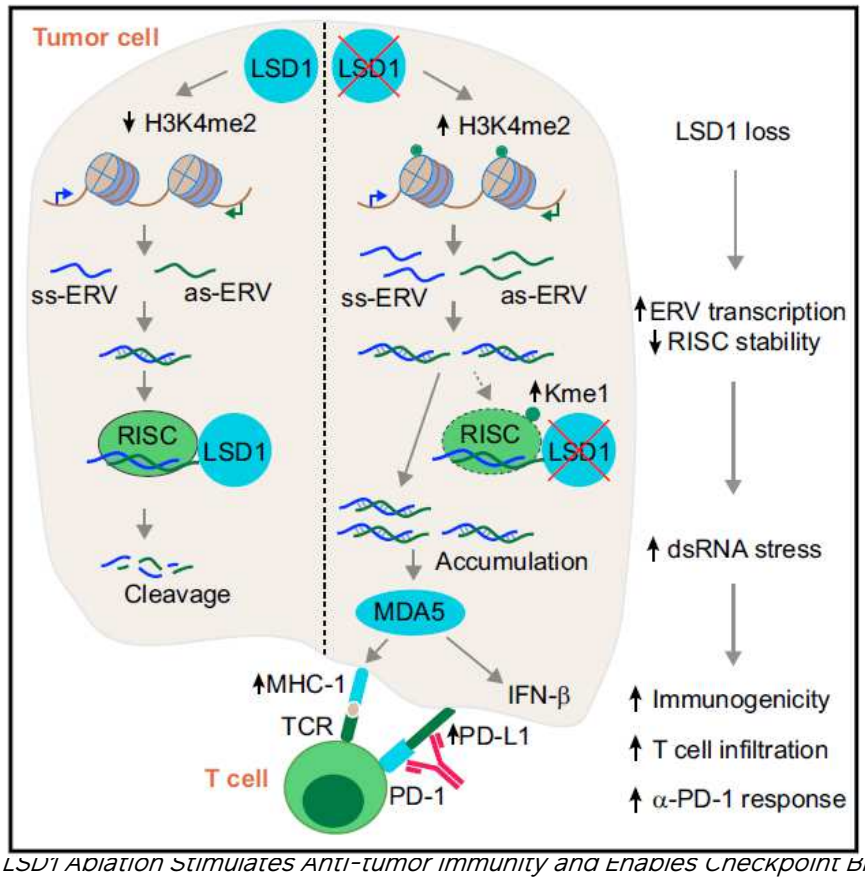
2- Oncology, a clear path ahead

The primary focus of Oryzon Genomics was initially the development in treatments for solid and blood cancers, notably through its partnership with ROCHE. Despite the withdrawal of ROCHE after three years of collaboration, we continue to view this development area as extremely pertinent and promising. Oryzon has recovered 100% of the rights to its drug in this therapeutic area.

2.1 Scientific rationale behind the development of epigenetics in cancer treatments

The activation of oncogenes or the deactivation of tumor suppressor genes have long been established as the basic mechanisms causing cancer. Nevertheless, different biochemical pathways essential to tumor growth are regulated by epigenetic phenomena.

A study published in CELL (*source : LSD1 Ablation Stimulates Anti-tumor Immunity and Enables Checkpoint Blockade ; Sheng et al., 2018, Cell 174, 1–15*) highlights the specific role of LSD1 in tumor proliferation. The ablation of the LSD1 histone demethylase stimulates the anti-tumor immunity of the T lymphocytes and slows tumor growth. Additionally, the depletion of LSD1 improves the immunogenicity of tumors and the infiltration of T lymphocytes in slightly immunogenic tumors and provokes significant responses in the melanoma of mice refractory to checkpoint blockade in connection with anti-PD-1 therapy.



Source: LSD1 Ablation Stimulates Anti-tumor Immunity and Enables Checkpoint Blockade; Sheng et al., 2018, Cell 174, 1–15

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2- Possible development in the cancer area

According to this same study, the induction of PD-L1 could suppress the functional activity of the TIL CD8+, thereby compromising the anti-tumor effect coming from the increase in TIL caused by the inhibition of LSD1. Based on this observation, it could equally be thought that the blocking of PD-1 would be synergetic with the inhibition of LSD1 in order to cause an anti-tumor immune response. The initial results in animals have confirmed this hypothesis.

Additionally, this same study demonstrated that the overexpression of LSD1 corresponds to a poor prognosis, with significantly lower overall survival time (potential biomarker). A low rate of LSD1 would consequently favor the infiltration of LTCD8+.

In summary, this study shows that (i) the loss of LSD1 in tumor cells stimulates the anti-tumor T immunity, (ii) the ablation of LSD1 improves the immunogenicity of the tumor and the infiltration of T cells and (iii) the inhibition of LSD1 overcomes the resistance to anti-PD-1 therapy in a mouse model of melanoma.

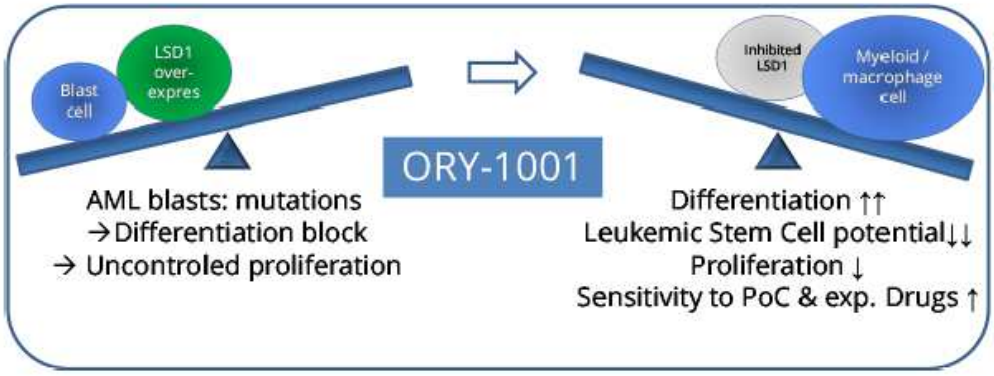
2.2 Acute myeloid leukemia as first indication

After having recovered the rights to ORY-1001, Oryzon worked to launch two phase IIa studies at the beginning of this year: one in acute myeloid leukemia, the other in small cell lung cancer.

2.2.1. Why target AML?

AML is a form of cancer of the blood and bone marrow that occurs when abnormal white cells begin to colonize the spinal fluid and interfere with the normal production of blood cells. The production of red cells and platelets falls, leading to fatigue due to anemia and a risk of bleeding along with an increased risk of infection. Prevalence ranges in principle between 1 and 9 persons out of 100,000.

Oryzon is targeting more specifically a sub-category of AML, mixed lineage leukemia (MLL). A study (also published in CELL) has shown that the inhibition of LSD1 could also slow the progression of leukemia. ORY-1001 specifically targets the leukemia cells without however modifying the HSPCs (Hematopoietic Stem and Progenitor Cells).



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2- Possible development in the cancer area

The different causes leading to MLL include the fusion of two genes: the MLL-AF9 and the gene-AF9. In patients suffering from MLL, it appears that the MLL-AF9 protein changes the state of the normal chromatin of the regulating hematopoietic stem cells.

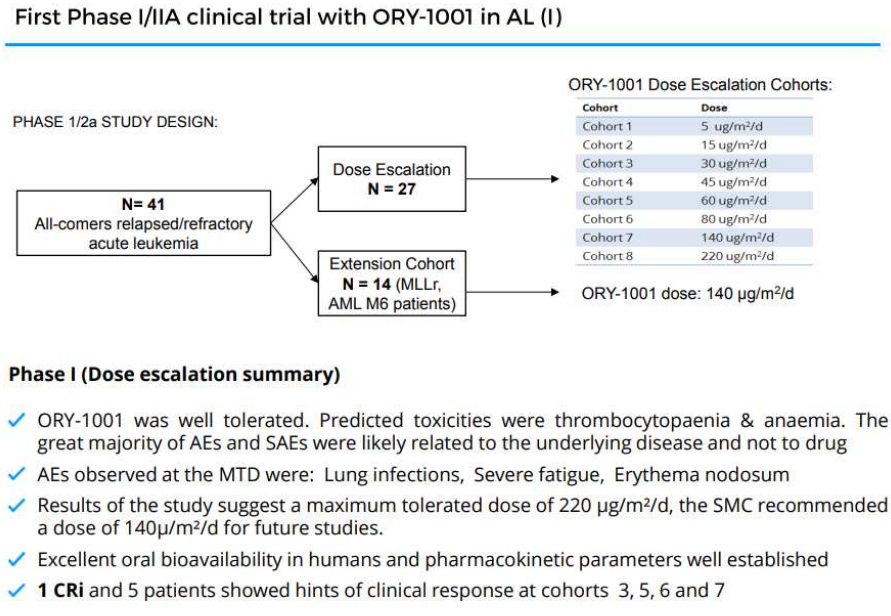
The majority of patients suffering from AML need treatment soon after the diagnosis, as the disease often progresses rapidly. The initial objective is to put the patient into remission. The long-term objective is to cure the disease through a bone marrow transplant. However, this is not always possible.

In general, persons suffering from AML immediately begin chemotherapy. Certain of the most widely used drugs include cytarabine (also called cytosine arabinoside or ara-C.) and an anthracycline (such as daunorubicin or idarubicin).

Stem cell transplants can be made after the chemotherapy as second phase of treatment.

2.2.2. Initial phase I results, phase IIa underway

Results from an initial phase I/IIa trial were announced at the 2016 ASH meeting. This study, which included 41 patients, showed bioavailability and pharmacokinetics parameters that did not raise any immediate questions for an orally-administered drug. Additionally, 22% of the treated population (6/27) showed a positive response rate, with even complete remission in one of the patients (suffering from normal AML). In parallel, 46% of the patients (6/13) with relapsing or refractory AML showed clinical activity. In the overall group, this anti-leukemia activity was seen in 12 patients. More specifically, partial remission in the bone marrow was seen in two cases out of the four evaluated in patients suffering from mixed lineage leukemia. In this same population, four out of six patients showed signs of morphological differentiation in the blast cells.



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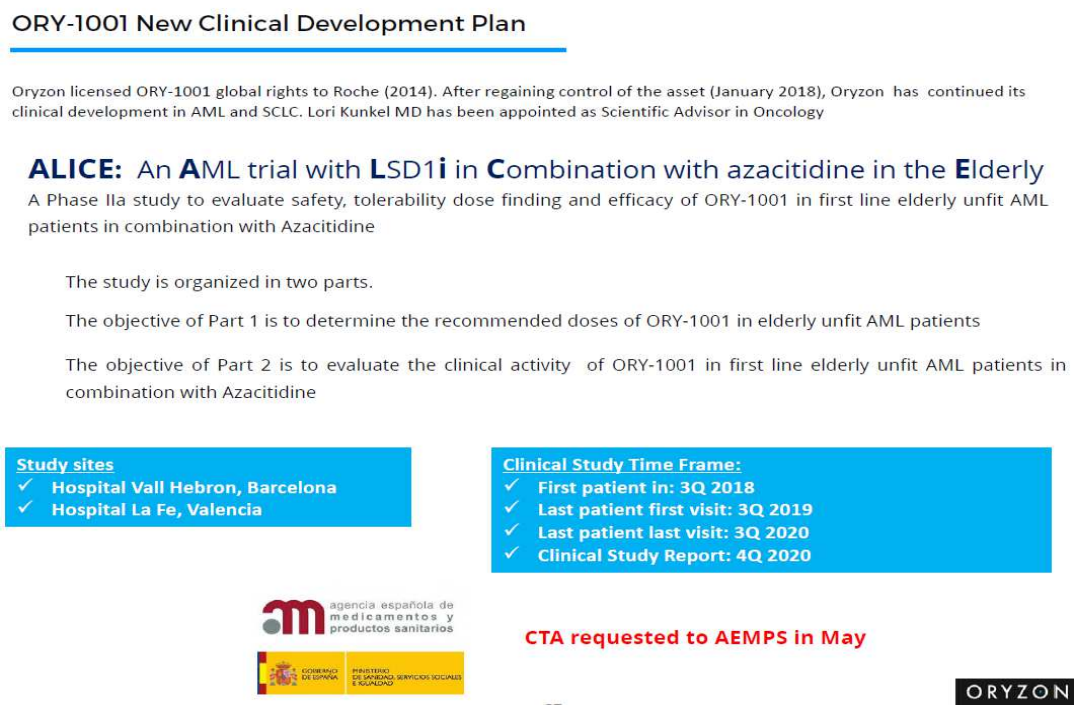
2- Possible development in the cancer area

Following this initial results showing activity for the drug, a second phase IIa trial is in the process of being launched, with initial results expected in mid-2019.



Source : Oryzon Genomics

As indicated above, azacitidine is a benchmark front-line treatment. Oryzon is seeking to combine the two drugs in order to first evaluate the toxicity but most importantly, the clinical activity that could be at the minimum compared to the literature. For our part, we would like to see clear stratification of the target population. Given the market trends in AML, we believe that the principal opportunity could be seen in patients suffering from mixed lineage leukemia. If, as was seen in the phase I trial, activity is visible in the broad population, the commercial position will be all the more sufficient.

2.3 A phase IIa study launched in SCLC

Lung cancers are divided between non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) based on the type of cell from which they develop.

Oryzon is currently targeting small cell lung cancer, which develops from cells that line the bronchi located in the center of the lungs.

The treatment of the patient depends on the stage of evolution of the pathology. Small cell lung cancer is divided into two stages, the limited stage and the extensive stage. Small cell lung cancer limited to a single side of the thorax can often be treated by radiotherapy. As indicated by its name, extensive-stage small cell lung cancer has spread in the lung. As in NSCLC, another classification (TNM) evaluates the stage of development, with stages ranging from I to IV.

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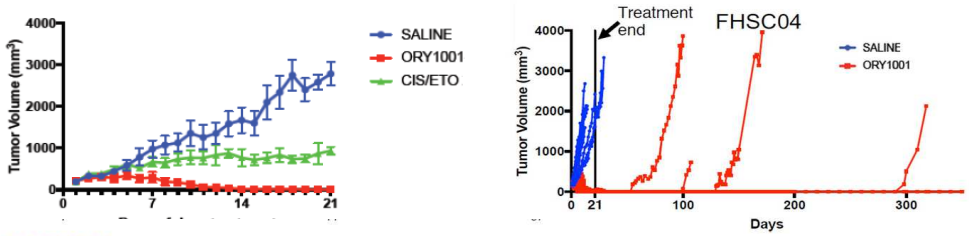
2- Possible development in the cancer area

2.3.1. Launch of a phase IIa study in SCLC

As of now, Oryzon is basing its efforts on initial animal results showing a high level of activity for ORY-1001, even if the level is variable. The following chart shows a FHSC04 model corresponding to a patient with SCLC with failure of first-line treatment (not stabilized). In six out of ten cases, mice of this type showed no relapse after 300 days.



CLEPSIDRA: A **C**ombination trial of **L**SD1 and **E**top-**P**latinum in **S**mall Cell Lung Cancer in Biomarker-**ID** **R**elapsed p**A**tients

The study is organized in two parts.

The objective of Part 1 is to determine the recommended doses of ORY-1001 in combination with platinum –etoposide chemotherapy in patients with relapsed, extensive-stage disease small cell lung cancer who are positive to candidate predictive biomarkers.

The objective of Part 2 is to evaluate clinical activity of ORY-1001 in combination with platinum –etoposide chemotherapy in patients with relapsed, extensive-stage disease small cell lung cancer who are positive to the candidate predictive biomarkers

Study sites
- ✓ Hospital Universitario y Politécnico La Fe Valencia Spain.
- ✓ Instituto Oncológico Dr. Rosell, Barcelona, Spain.
- ✓ Oncology Department. Hospital 12 Octubre, Madrid, Spain.
- ✓ Centro Oncológico Clara Campal, Madrid, Spain.

Clinical Study Time Frame:
- ✓ First patient in: 4Q 2018
- ✓ Last patient first visit: 4Q 2019
- ✓ Last patient last visit: 4Q 2020
- ✓ Clinical Study Report: 1Q 2021

agencia española de medicamentos y productos sanitarios

CTA requested to AEMPS on 11th July 2018

Source : Oryzon Genomics

2.3.2. Rationale behind the combination with immuno-oncology

As highlighted above, there appears to be a genuine scientific rationale for a combination of an epigenetic approach involving LSD1 and a check-point inhibitor. More specifically, the article by Sheng et al indicated that the loss of LSD1 in the tumor cells increases the expression of endogenous retroviruses (ERVs) and reduces the expression of gene silencing elements generated by the RNA. This leads to stress in the double branded RNA and the activation of type 1 interferon that improves the tumor immunogenicity and limits tumor growth. Additionally, the article also highlights an interesting correlation between the expression of LSD1 and the infiltration of CD8+ T lymphocytes.

This article therefore reinforces the initial development of certain combinations of epigenetic agents. An example of this can be found in the pipeline of Epizyme, which includes the development of tazemetostat in combination with Tecentriq in NHL (non-Hodgkin's lymphoma) and NSCLC.

Given the characteristics of LSD1, we consequently believe that a development strategy involving a combination with an immuno-oncology drug would be pertinent. We can therefore not rule out the possibility than in advance of development and commercial partnerships for ORY-1001, ORYZON could seek to work with other players in order to confirm the scientific rationale here. A global, regional or therapeutic partnership agreement could subsequently be signed.

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3- VALUATION

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3- Valuation

We are focusing essentially on the four most advanced indications at present, even if we could imagine broader development in the near future. As such, we have integrated into our model Alzheimer's diseases and SPMS in the CNS area and AML and lung cancer in the cancer area. New indications could be targeted over the short term, with notably a large range of possibilities in the CNS area. For information purposes, we will evaluate two indications (Huntington's and Parkinson's) that we have not included at this point.

3.1 ORY-2001 in Alzheimer's: the company's spearhead

After the positive and highly promising preclinical and phase I results, Oryzon launched a phase IIa study called ETHERAL for the development of ORY-2001 in Alzheimer's disease in April 2018. We anticipate initial intermediate results from this phase II study in mid-2019.

We have made the following assumptions:

- We only value the European and US markets at this point, even if China and Japan, which are currently experiencing rapid population aging, could subsequently become attractive markets for ORY-2001.
- We assume that approval could be obtained in 2025.
- We estimate that 5.4 million Europeans and 6.8 million Americans have Alzheimer's disease in 2018. We anticipate a sale price of €1,000/yr in Europe and €1,700/yr in the United States. Even if generic versions of aricept/Namenda are available at a cost of around $300/yr, we believe that Oryzon could justify a substantial premium compared to the generics. Additionally, the number of persons suffering from Alzheimer's in these two geographical zones is growing by +2.5% per year.
- Based on the characteristics of ORY-2001 and the initial information provided by the company regarding its development, we have decided to limit this addressable market to persons with mild to moderate forms of the disease (48%) and undergoing treatment (57%). While we have cautiously decided to maintain these two percentages stable over time, it is possible that improvements in prevention and screening in the countries under consideration could lead to an increase in populations receiving treatment.
- Given the size of the Alzheimer's disease market and the costs involving in the launching of a large-scale phase III study in order to obtain approvals in Europe and the United States, we have assumed that the company will sign a commercialization agreement with a major partner in both the United States and Europe.
  - We have made the following assumptions in our valuation of this agreement:

    - Payment of a €40m upfront.

    - Milestone payments of €50m and €100m, with the first paid at the time of approval and initial sales (2025) and the second paid after crossing the threshold of €500m in cumulative sales, which we estimate will occur in 2029.

    - 15% royalties on sales, rising to 17% in the year following the crossing of the threshold of €500m in cumulative sales.

    - The full cost of the phase III development of ORY-2001 will be assumed by the partner.

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3- Valuation

- We integrate a prudent probability of success (POS) of 11.6% to reflect the product's early stage of development and to take into account the numerous failures in phases II and III making up the history of development in Alzheimer's (source: Bio Industry).

- We use as discount rate a WACC of 13.5% corresponding to the one-year average of the 10-yr OAT, a risk premium for the French market of 5.64% as calculated by Factset and a beta of 2.25.

Alzheimer	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population Alzheimer (m)	5,4	5,6	5,7	5,9	6,0	6,1	6,3	6,5	6,6	6,8	7,0	7,1	7,3	7,5
% formes modérées	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*
Population Alzheimer modérés	2,6	2,7	2,7	2,8	2,9	3,0	3,0	3,1	3,2	3,3	3,3	3,4	3,5	3,6
Sous traitement	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*
Pénétration du marché	0	0	0	0	0	0	0	0,01	0,05	0,1	0,2	0,25	0,25	0,25
Patients en traitement	-	-	-	-	-	-	-	17 668	90 548	185 622	380 526	487 549	499 738	512 231
Prix annuel/patient US	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*	*1698 €*
Ventes EURm (US)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**30**	**154**	**315**	**646**	**828**	**849**	**870**

Alzheimer	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population Alzheimer (en m)	6,8	7,0	7,1	7,3	7,5	7,7	7,9	8,1	8,3	8,5	8,7	8,9	9,1	9,4
% formes modérées	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*	*48,00%*
Population Alzheimer modérés	3,3	3,3	3,4	3,5	3,6	3,7	3,8	3,9	4,0	4,1	4,2	4,3	4,4	4,5
Sous traitement	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*	*57,0%*
Pénétration du marché	0	0	0	0	0	0	0	0	0,01	0,05	0,1	0,2	0,25	0,25
Patients en traitement	-	-	-	-	-	-	-	-	22 637	116 014	237 829	487 549	624 672	640 289
Prix annuel/patient Europe	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*	*1019 €*
Ventes EURm (UE)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**23**	**118**	**242**	**497**	**636**	**652**

m€	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Ventes	-	-	-	-	-	-	-	**30**	**177**	**433**	**888**	**1325**	**1485**	**1522**
Upfronts touchés	-	-	-	-	**40**	-	-	**80**	-	**50**	-	**100**	-	-
Royalties	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**5**	**27**	**65**	**133**	**225**	**252**	**258,8**
COGS	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R&D	*-6,0*	*-6,0*	*-6,0*	*-6,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	0,0
SG&A	-	-	-	-	-	-	-	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	-0,5
EBIT	**-6,0**	**-6,0**	**-6,0**	**-6,0**	**40,0**	**0,0**	**0,0**	**84,1**	**26,1**	**114,6**	**132,8**	**324,7**	**252,0**	**258**
Impôts (CIR + tax)	0,90	0,90	0,90	0,90	-6,00	-	-	-12,61	-3,91	-17,18	-19,92	-48,71	-37,80	-38,75
var BFR	-	0,0	0,0	0,0	1,0	-1,0	0,0	2,8	1,7	7,7	10,1	13,4	1,5	0,9
Capex	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0
FCF	**-6**	**-6**	**-6**	**-6**	**34**	**-2**	**-1**	**73**	**23**	**104**	**122**	**288**	**215**	**220**
FCF cumulés actualisés	353													
Valeur résiduelle actualisée	0													
NPV	**353**													
PoS (Probabilité de succès)	12%													
rNPV (NPV ajusté à la PoS)	**41**													

Source : Invest Securities

3.2 SPMS, a bold ambition

As mentioned above, Oryzon's second priority indication in the CNS area is multiple sclerosis (MS). We believe that the principal differentiating factor that would enable the company to benefit from not only a premium in price terms but also to be a target for a sector player would be the "secondary progressive" (SPMS) indication.

We have made the following assumptions:

- We only value the European and US markets at this point, even if China and Japan, which are currently experiencing rapid population aging, could subsequently become attractive markets for ORY-2001.

- We assume a launch of clinical development for the product at the end of 2019. This could lead to initial sales in Europe and the United States in 2026.

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- According to an article in *Neurology* last April (*Estimated prevalence of secondary progressive multiple sclerosis in the USA and Europe: results from a systematic literature search*), we model a prevalence in the United States of 37.1 per 100,000 and an average of 30.7 per 100,000 in Europe. We assume in our estimates an average annual price per patient of €54k/yr in the United States and €40k/yr in Europe. Nevertheless, it is clear that the price difference between SPMS and Alzheimer's cannot be so large given that we are talking about the same drug. We have used estimates that we believe at this point to be coherent in terms of prices based on the medical need to be met if results prove positive.

- Our assumptions are cautious and assume stability in the prevalence of the disease over time as well as in the percentage of persons diagnosed and therefore seeking treatment (90%), even if currently trends could suggest a significant increase in these figures by the time the reaches the market .

- Given the opportunity represented by this indication if results prove to be positive, we once again estimate that the company will sign a partnership agreement after the phase II results in order to finance a large-scale phase III study.

We have made the following assumptions concerning this partnership:

- €50m upfront.
- Milestone payments totaling €480m,
- 15% royalties on sales, rising to 17% after €1bn in sales
- The full cost of the phase III development of ORY-2001 will be assumed by the partner.

- We include a cautious probability of success (POS) of 11.1% to reflect the early stage of development of the product (*source*: Bio Industry).

SPMS	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population US	327,8	330,2	332,6	334,9	337,2	339,5	341,8	344,1	346,3	348,5	350,6	352,8	354,8	356,9
PrevalenceMS	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*	*0,049%*
Population atteinte de SPMS	0,1216	0,1225	0,1234	0,1242	0,1251	0,1260	0,1268	0,1276	0,1285	0,1293	0,1301	0,1309	0,1316	0,1324
SPMS	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095	0,1095
Taux de pénétration	0	0	0	0	0	0	0		0,01	0,05	0,1	0,15	0,2	0,2
Patients en traitement	-	-	-	-	-	-	-	-	1 095	5 473	10 947	16 420	21 894	21 894
Prix annuel/patient US	*53 913 €*	*53 913 €*	*53 913 €*	*53 913 €*	*53 913 €*	*53 913 €*	*53 913 €*	*53 913 €*	53 913 €	*53 913 €*	*53 913 €*	*53 913 €*	*53 913 €*	*53 913 €*
Ventes EURm (US)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**59**	**295**	**590**	**885**	**1180**	**1180**

SPMS	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population EUR (ouest)	418,6	420,2	421,6	422,9	424,2	425,4	426,6	427,8	428,9	430,0	431,1	432,2	433,3	434,3
Prevalence	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*	*0,039%*
Population atteinte de Huntington	0,1287	0,1292	0,1296	0,1300	0,1304	0,1308	0,1311	0,1315	0,1319	0,1322	0,1325	0,1329	0,1332	0,1335
Population présentant les symptômes visés	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158	0,1158
Taux de pénétration	0	0	0	0	0	0	0		0,01	0,05	0,1	0,12	0,15	0,15
Patients en traitement	-	-	-	-	-	-	-	-	1 158	5 791	11 582	13 899	17 373	17 373
Prix annuel/patient UE	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*	*40 435 €*
Ventes EURm (UE)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**47**	**234**	**468**	**562**	**702**	**702**

Source : Invest Securities

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m€	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Ventes	-	-	-	-	-	-	-	-	106	529	1059	1447	1883	1883
Upfronts touchés	-	-	-	-	50	-	-	80	-	100	100	-	200	-
Royalties	0	0	0	0	0	0	0	0	16	79	180	246	320	320
COGS	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R&D	*-6,0*	*-6,0*	*-6,0*	*-6,0*	*-6,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*
SG&A	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*	*-1,0*
EBIT	-7,0	-7,0	-7,0	-7,0	43,0	-1,0	-1,0	79,0	14,9	178,4	278,9	245,0	519,1	319
Impôts (CIR + tax)	0,90	0,90	0,90	0,90	-5,55	-	-	-11,85	-2,23	-26,76	-41,84	-36,75	-77,86	-47,86
Var BFR	-	-	-	-	1,3		-	2,0	-0,6	-13,1	-13,2	-7,2	-15,9	5,0
Capex	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5	-1,5
FCF	-8	-8	-8	-8	37	-4	-3	68	10	137	222	200	424	275
FCF cumulés actualisés	2415													
Valeur résiduelle actualisée	0													
NPV	2415													
PoS (Probabilité de succès)	11%													
NPV (NPV ajusté à la PoS)	268													

Source : Invest Securities

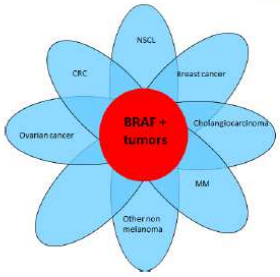
3.3 Potentially attractive markets in a range of CNS indications not included for the moment

In parallel, Oryzon is evaluating the interest in launching clinical development in a range of CNS indications. We have chosen two that we consider at first glance to be the most logical: Huntington's and Parkinson's disease. The mechanism of action of ORY-2001, potentially in combination with other drugs, could treat the psychiatric symptoms of these diseases.

Basket Trial in CNS, an innovative concept

✓ Compelling preclinical data support the concept of a basket trial of ORY-2001 for treatment of aggressiveness and other behavioral alterations in neurodegenerative and psychiatric disorders

Basket Trials in Oncology



Example: Vemurafenib is an oral inhibitor of *BRAF* that has greater selectivity for the $BRAF^{V600}$ mutant form of the kinase than for wild-type *BRAF*, which had been previously approved for patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma.

Vemurafenib was targeted at a single variant in a variety of cancers with different primary disease sites and histologies, thereby defining disease-specific baskets.

Basket Trial in CNS

Aggression is observed in patients with different CNS diseases
A principal cause of aggressiveness is response to stress. Genes involved in stress management include immediate-early genes (IEGs). Epigenetic changes and IEG induction play a crucial role in these behavioral responses

ORY-2001 normalizes the response of IEGs to stress in the SAMP8 AD model

Source : Oryzon Genomics

Nevertheless, given the very early stage of development, we have not included any of these potential new indications in our model. We have valued these two additional markets for information purposes only and we currently view them as free options in our valuation.

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We have made the following assumptions:

- We only value the European and US markets at this point, even if China and Japan, which are currently experiencing rapid population aging, could subsequently become attractive markets for ORY-2001.

- We assume a launch of clinical development for the product at the end of 2019. This could lead to initial sales in Europe and the United States in 2026.

- We assume that nearly one million Americans and 1.2 million Europeans currently suffer from Parkinson's disease (source: Parkinson's Foundation). We assume in our estimates an average annual price per patient of €952/yr in the United States and €571/yr in Europe. Our assumptions are cautious and integrate stability in the prevalence over time as well as in the percentage of persons diagnosed and therefore seeking treatment (70%), even if current trends (population aging, increased prevention) could suggest a significant increase in these figures by the time the product reaches the market.

- Given the size of the market represented by Parkinson's and Huntington's disease, we once again estimate that the company will sign a strategic partnership agreement after positive phase II results in order to be able to be able to finance a large-scale phase III study. We have made the following assumptions concerning this partnership:

ORY-2001 and which we of Huntington's and

- An upfront payment of €24m corresponding to 5% of peak sales of on the signing of the contract.
- Milestone payments of €50m in connection with initial sales (2026) €100m after exceeding the threshold of €300m in cumulative sales, estimate will take place in 2029.
- 15% royalties on sales, rising to 17% in the year when the threshold €300m in cumulative sales is exceeded
- **The full cost of the phase III development of ORY-2001** in Parkinson's **will be assumed by the partner**.

- We integrate a cautious probability of success (POS) of 11.7%, in line with the Alzheimer's indication.

m€	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Ventes	-	-	-	-	-	-	-	-	24	119	238	359	481	483
Upfronts touchés	-	-	-	-	-	24	-	-	50	-	-	100	-	-
Milestones	0	-	-	-	-	-	-	-	4	18	36	61	82	82,1
COGS	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R&D	*-3,0*	*-3,0*	*-3,0*	*-3,0*	*-3,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*
SG&A	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*	*-0,5*
EBIT	**-3,5**	**-3,5**	**-3,5**	**-3,5**	**-3,5**	**23,6**	**-0,5**	**-0,5**	**53,0**	**17,3**	**35,3**	**160,6**	**81,3**	**82**
Impôts (CIR + tax)	0,45	0,45	0,45	0,45	0,45	-3,55	0,00	0,00	-7,96	-2,59	-5,29	-24,08	-12,19	-12,24
var BFR	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Capex							-	-	-	-	-	-	-	-
FCF	**-3**	**-3**	**-3**	**-3**	**-3**	**20**	**-1**	**-1**	**45**	**15**	**30**	**136**	**69**	**69**
FCF cumulés actualisés	116													
Valeur résiduelle actualisée	0													
NPV	**116**													
PoS (Probabilité de succès)	12%													
rNPV (NPV ajusté à la PoS)	**13**													

Source : Invest Securities

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3.4 Two promising development programs in oncology

The initial results for ORY-1001 in oncology now justify its development in acute leukemia and small cell lung cancer. A phase IIa study is in the process of being launched in these two indications and we estimate that the initial results will be announced in one year.

We have chosen a rNPV method running through 2031 in order to evaluate Oryzon's pipeline in oncology.

We have made the following assumptions:

- We only value the European and US markets at this point, even if China and Japan, which are currently experiencing rapid population aging, could subsequently become attractive markets for ORY-1001.

- In parallel, we estimate that the definitive results of the phase IIa trial of ORY-2001 in Alzheimer's should be announced at the end of 2020, thereby allowing the launch of a phase III study at the beginning of 2022 in order to obtain European approval, CE marking and FDA approval in 2025.

- As the two indications are niche markets on which the company is targeting high market shares, we estimate that it will be able to use the funds coming from partnership agreements in Alzheimer's to notably self-finance the launch of a phase III study and the commercial launch of the product :

  - R&D costs on the order of €10m per year over the period 2023-2025, corresponding to the costs of the launch of two phase III studies.

  - COGS equal to around 30% sales, made necessary by the in-house commercialization of the product

  - SG&A equal to around 25% sales reflecting the required support functions in connection with the commercialization of the product.

- We integrate a cautious probability of success (POS) of 8,1% to reflect the early stage of development of the product and to take into account the difficulty in commercializing solutions on markets that currently correspond to medical deserts.

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Acute Leucemia	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population US	327,8	330,2	332,6	334,9	337,2	339,5	341,8	344,1	346,3	348,5	350,6	352,8	354,8	356,9
Prevalence	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*
Population atteinte de AL	0,0197	0,0198	0,0200	0,0201	0,0202	0,0204	0,0205	0,0206	0,0208	0,0209	0,0210	0,0212	0,0213	0,0214
Population atteinte de AL présentant le MLL	0,0020	0,0020	0,0020	0,0020	0,0020	0,0020	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021
Population en rechute ou intolérante	0,0016	0,0016	0,0016	0,0016	0,0017	0,0017	0,0017	0,0017	0,0017	0,0017	0,0017	0,0017	0,0017	0,0018
Taux de pénétration	0	0	0	0	0	0	0	0,01	0,2	0,4	0,6	0,6	0,6	0,6
Patients en traitement	-	-	-	-	-	-	-	17	341	686	1 035	1 041	1 047	1 053
Prix annuel/patient US	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*
Ventes EURm (US)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**20**	**41**	**62**	**62**	**63**	**63**

Acute Leucemia	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population EUR (ouest)	418,6	420,2	421,6	422,9	424,2	425,4	426,6	427,8	428,9	430,0	431,1	432,2	433,3	434,3
Prevalence	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*	*0,01%*
Population atteinte de AL	0,0251	0,0252	0,0253	0,0254	0,0255	0,0255	0,0256	0,0257	0,0257	0,0258	0,0259	0,0259	0,0260	0,0261
Population atteinte de AL présentant le MLL	0,0025	0,0025	0,0025	0,0025	0,0025	0,0026	0,0026	0,0026	0,0026	0,0026	0,0026	0,0026	0,0026	0,0026
Population en rechute ou intolérante	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021	0,0021
Taux de pénétration	0	0	0	0	0	0	0	0,01	0,2	0,4	0,6	0,6	0,6	0,6
Patients en traitement	-	-	-	-	-	-	-	21	422	846	1 273	1 276	1 279	1 282
Prix annuel/patient UE	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*
Ventes EURm (UE)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**20**	**41**	**61**	**61**	**61**	**62**

Small Cell Lung Cancer	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population US	327,8	330,2	332,6	334,9	337,2	339,5	341,8	344,1	346,3	348,5	350,6	352,8	354,8	356,9
Prevalence SLC	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*	*0,05%*
Population atteinte de Lung Cancer	0,1639	0,1651	0,1663	0,1674	0,1686	0,1698	0,1709	0,1720	0,1731	0,1742	0,1753	0,1764	0,1774	0,1784
Population atteinte de SCLC	0,0246	0,0248	0,0249	0,0251	0,0253	0,0255	0,0256	0,0258	0,0260	0,0261	0,0263	0,0265	0,0266	0,0268
Taux de pénétration	0	0	0	0	0	0	0	0,01	0,1	0,15	0,2	0,25	0,25	0,25
Patients en traitement	-	-	-	-	-	-	-	258	2 597	3 920	5 260	6 614	6 653	6 691
Prix annuel/patient US	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*	*60 000 €*
Ventes EURm (US)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**15**	**156**	**235**	**316**	**397**	**399**	**401**

Small Cell Lung Cancer	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Population EUR (ouest)	418,6	420,2	421,6	422,9	424,2	425,4	426,6	427,8	428,9	430,0	431,1	432,2	433,3	434,3
Prevalence SLC	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*	*0,03%*
Population atteinte de Lung Cancer	0,1298	0,1302	0,1307	0,1311	0,1315	0,1319	0,1322	0,1326	0,1330	0,1333	0,1337	0,1340	0,1343	0,1346
Population atteinte de SCLC	0,0195	0,0195	0,0196	0,0197	0,0197	0,0198	0,0198	0,0199	0,0199	0,0200	0,0200	0,0201	0,0201	0,0202
Taux de pénétration	0	0	0	0	0	0	0	0,01	0,1	0,15	0,2	0,25	0,25	0,25
Patients en traitement	-	-	-	-	-	-	-	199	1 995	3 000	4 010	5 025	5 037	5 049
Prix annuel/patient UE	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*	*48 000 €*
Ventes EURm (UE)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**10**	**96**	**144**	**192**	**241**	**242**	**242**

m€	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Ventes	-	-	-	-	-	-	-	**27**	**292**	**461**	**631**	**762**	**765**	**769**
COGS	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*-8,1*	*-87,7*	*-138,3*	*-189,4*	*-228,5*	*-229,6*	*-230,6*
R&D	*-3,0*	*-3,0*	*-3,0*	*-8,0*	*-8,0*	*-10,0*	*-10,0*	*-10,0*	*-3,0*	*-3,0*	*-3,0*	*-3,0*	*-3,0*	*-3,0*
SG&A	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*0,0*	*-6,8*	*-73,1*	*-115,2*	*-157,8*	*-190,4*	*-191,3*	*-192,1*
EBIT	**-3,0**	**-3,0**	**-3,0**	**-8,0**	**-8,0**	**-10,0**	**-10,0**	**2,2**	**128,5**	**204,4**	**281,1**	**339,8**	**341,3**	**342,9**
Impôts (CIR + tax)	0,45	0,45	0,45	1,20	1,20	1,50	1,50	1,17	-18,83	-30,22	-41,71	-50,52	-50,75	-50,98
var BFR	-	-	-	-	-	-	-	-0,7	-6,6	-4,2	-4,3	-3,3	-0,1	-0,1
Capex	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	-1,0	*-1,0*
FCF	**-4**	**-4**	**-4**	**-8**	**-8**	**-10**	**-10**	**2**	**102**	**169**	**234**	**285**	**290**	**291**
FCF cumulés actualisés	431													
Valeur résiduelle actualisée	0													
NPV	**431**													
PoS (Probabilité de succès)	8%													
rNPV (NPV ajusté à la PoS)	**35**													

Source : Invest Securities

As a conclusion, our valuation integrates the 2 products in the 4 indications. We consider, as our hypothesis, a partnership in the CNS but a development in house in the Oncolgy indications. Our valuation, based on future financing needs (see IS methodology), achieves € 408m, or € 9.3 per share.

SOTP	in m€	€ per share
Alzheimer	41	0,9
SPMS	268	6,1
Oncology	35	0,8
CF adjusted*	64	1,5
Valuation	**408**	**9,3**
number of adjsuted actions*	43,7	

* including the financing needs in 2018-20

Source : Invest Securities

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ORYZON GENOMICS

SWOT ANALYSIS

STRENGTHS

- An epigenetic platform
- Numerous clinical development programs
- Solid cash position

WEAKNESSES

- No partner
- Numerous failures in the CNS area

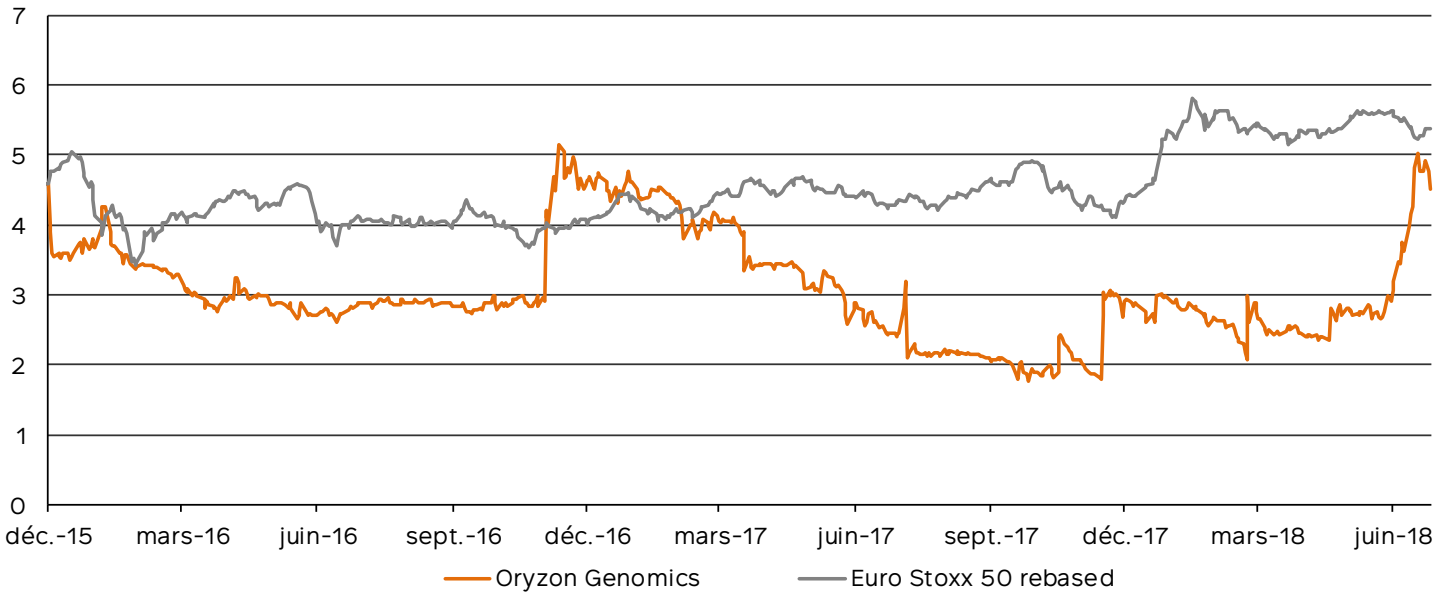
OPPORTUNITIES

- A potential target

THREATS

- Increased competition

SHARE PRICE PERFORMANCE OVER FIVE YEARS



CONFLICTS

	Corporate Finance	Treasury stocks holding	Prior communication to company	Liquidity contract	Liquidity contract	Listing Sponsor	Research Contract
Oryzon	No	No	Yes	No	No	No	Yes

DICSLAIMER

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